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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,733	10/01/2003	Kevin H. Gardner	UTSD:1510	4887
23379	7590	08/06/2008	EXAMINER	
RICHARD ARON OSMAN 4070 CALLE ISABELLA SAN CLEMENTE, CA 92672				NOAKES, SUZANNE MARIE
ART UNIT		PAPER NUMBER		
1656				
NOTIFICATION DATE			DELIVERY MODE	
08/06/2008			ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

RICHARD@SCI-TECH.COM
jan@sci-tech.com

Office Action Summary	Application No.	Applicant(s)	
	10/677,733	GARDNER ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 05 May 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 3-5 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 3 and 5 is/are rejected.

7) Claim(s) 4 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____ .	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 05 May 2008 has been entered.

Status of Application

2. The remarks, declaration and amendments to the claims filed 11 April 2008 are acknowledged and have been entered. Applicants have cancelled claim 6; thus, claims 3-5 are pending and subject to examination on the merits.

It is noted that claims 3 and 5 correspond to canceled claim 1 (6/21/06), and claim 4 corresponds to canceled claim 2 (6/21/06). Said claim 1 has been before the Board of Patent Appeals and Interference (see BPAI decision 19 September 2007).

The Examiner for the instant application has changed since the last Final Office action (dated 11 December 2007). All further correspondence should be addressed to the Examiner below.

Withdrawal of Rejections/Objections

3. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fesik (WO 97/18471) in view of any one of U. S. patents 5,843,683 (Edery *et al.*); 6,291,429 (Takahaski *et al.*); 6,436,654 (Berkenstam *et al.*) for the reasons of record (see previous Office actions from: 11 December 2007, 05 September 2006 and 21 February 2006 and the Board of Patent Appeals and Interferences decision of 19 September 2007, which affirms the Final rejection of 05 September 2006). All references have been cited previously on PTO-892 (02/21/06).

Response to Amendment

6. The Declaration under 37 CFR 1.132 by Professor Kevin H. Gardner, filed 11 April 2008, is insufficient to overcome the rejection of claims 3 and 5 based upon 35 U.S.C. 103(a) as set forth in the last Office action because of the following reasons.

Professor Gardner asserts that the previous Office action (11 December 2007) is not reflective of the ordinary skill and understanding in the art and that “Its conclusions are unwarranted and erroneous, and its analysis contains multiple and fundamental overstatements and technical inaccuracies.” (see Declaration, point 3). In support of these assertions, Prof. Gardner states that the Office action relies on two suppositions which are both technically incorrect; that being that it would be obvious to screen PAS domains because they all contain ligand binding sites and that solution NMR is an obvious choice for a screening method to identify the protein-binding ligands for any target (see point 4, p. 1). It is asserted that the Examiner’s argument that reasons a skilled artisan would have known of the presence of the ligand-binding cavity because the protein has an activity in solution, is misleading and inaccurate (see point 5, pp. 1-2). Prof. Gardner asserts that most PAS domains are not naturally regulated by small molecule ligands or cofactors and that the art teaches that most PAS domains function as constitutive protein/protein interaction domains in their current settings, independent of small molecule regulation (see point 5, p. 2).

However, it is asserted that this is neither a misleading or inaccurate statement. If it is known that the protein of interest does or does not have various activities in the presence or absence of certain ligands or cofactors which contribute the proteins overall function, then one skilled in the art would reasonably conclude that it must therefore likely bind to the protein/PAS domain (also see previous Office action, p. 3, last paragraph to p. 4). In addition, given the fact that many PAS domains do require cofactors to initiate allosteric control of the proteins function (e.g. FixL which uses the

heme to detect oxygen levels, see specification p. 1), one skilled in the art would also reasonably conclude that other co-factors or ligands may be required by other PAS domains. In addition, given what was known in the art at the time of filing, it was accepted that PAS domains are signaling modules that monitor changes in environmental conditions via core-bound molecules (Taylor et al, 1999; pg 480, parg 1; pg 488, parg 3; pg 490, parg 2, 1st column). Thus, Taylor et al. teach that, more likely than not, any PAS domain will bind a ligand in its core. Finally, the position taken by the Board of Patent Appeals and Interference was that they did not agree that one skilled in the art would not have suspected that PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding" because Takahaski suggests a method for identifying ligands for a PAS protein having a hydrophobic core, Edery describes an assay method for identifying compounds that regulate a PAS domain protein's activity. Thus, they conclude that despite the fact that these proteins have tightly packed cores with no pre-formed cavities it was still suggested that these PAS domain proteins be utilized for ligand screening (see, e.g., Takahaski, at col. 9, ll. 14-16; Edery, at col. 46-50) - See BPAI decision, p. 6.

Prof. Gardner also asserts that while the accepted view in the field is that developing protein/protein inhibitor is difficult but not impossible, the instant invention is nonetheless non-obvious because core targeting of inhibitors raises additional challenges. Namely, a) without an *a priori* formed cavity there would be an overwhelming expectation that our targeted core ligand binding sites would not even

exist; b) it would be uncertain and unpredictable whether ligand binding to interior sites could provoke an allosteric change that affects a protein's function; and c) compounds that target internal sites bind much slower and thus possess slower "on" rates.

However, given that proteins in solution are not static and "breathe" while in solution, if one understands that a given protein may bind a small molecule ligand, even in the absence of an *a priori* binding cavity, it will also be obvious that it must necessarily bind somewhere on the protein; either internally or externally. Furthermore, most known PAS domains have cofactors that bind to the hydrophobic core regions (see Taylor et al. 1999, p. 490, 1st column, 2nd full paragraph) making internal binding the likely choice. While it is somewhat more difficult to detect binding internally because it takes longer for binding to occur (e.g. to detect on-rates of the ligand), it still is not by any means impossible, which is a point acknowledged by Prof. Gardner. Furthermore, binding affinities for a ligand, just because said ligand binding occurs internally rather than externally, does not necessarily correlate to the ligand's true binding affinity to the protein (e.g. its K_m). Rather, said binding affinity will be a direct consequence of the ligand-protein interaction and how well the candidate ligand fits into the binding pocket or interacts with the protein's ligand-binding site residues.

Prof. Gardner asserts that the Examiner is mistaken by asserting that NMR, as taught by Fesik et al., is one of the most sensitive methods available to probe protein-ligand interactions. Rather, it is asserted that NMR is one of the least sensitive methods compared to other methods such as thermal shift assays or a PerkinElmer –

AlphaScreen. Furthermore, it also requires magnitudes more protein requiring isotopically labeled protein which is economically cost-prohibitive (see point 7, pp. 2-3).

However, it is noted that Prof. Gardner subsequently does point out that NMR is a very good technique to detect low binding affinity ligands and it is one of the few methods which can give any information regarding where the ligand binding occurs on a given protein (see p. 3, 2nd full paragraph). It is asserted that these reasons rather support why one skilled in the art might be motivated to use said technique. Furthermore, the fact that it might be costly to produce PAS domains for study with NMR does not make it non-obvious to use said technique. It is noted that the fact that while a combination might not be made by businessmen for economic reasons does not mean that a person of ordinary skill in the art would not make the combination because of some technological incompatibility. In re Farrenkopf , 713 F.2d 714, 219 USPQ 1 (Fed. Cir. 1983) (Prior art reference taught that addition of inhibitors to radioimmunoassay is the most convenient, but costliest solution to stability problem. The court held that the additional expense associated with the addition of inhibitors would not discourage one of ordinary skill in the art from seeking the convenience expected therefrom.). (see MPEP 2145).

Prof. Gardner also asserts while the Examiner discusses the effect of dynamics on NMR spectra of proteins that said Examiner is right that these effects can lead to the disappearance of peaks in spectrum of a target, but these would discourage a practitioner in the field from proceeding with further studies of a protein target. The lack of peaks in this way is highly correlated with difficulty in further analysis and screens.

One skilled in the art would not proceed with screening a sample using a certain method when that method does not provide the data needed to establish if ligands are binding or not. (see point 8, bottom of p. 3).

However, the presence and absence of peaks would not necessarily discourage one of skilled in the art from using NMR. As stated, because it is known that the protein does in fact have an activity in solution, e.g. it is known that the protein does have a binding activity in solution, one need not dwell on the fact the initial NMR spectrum when the ligand is not present does not provide a ligand binding peak. Rather, it is the "after" spectrum, e.g. after the ligand has bound which will give the greatest information relative to the before spectrum because there will have to a conformational change in the protein in order to accommodate binding of the ligand and this will be revealed in the "after" NMR spectrum.

Finally, Prof. Gardner asserts that the Examiner has contradicted himself by stating that: "The major advantage of the NMR method over any other screening method is that it observes the binding of the small molecule directly to the target protein in its native environment, i.e. in aqueous solution There is no reason to believe that the most abundant conformation in solution which is observed by NMR is the most relevant conformation for binding a small molecule or a large target molecule." Action, p. 3". It is asserted that these sentences are inconsistent wherein the first argues that NMR methods should be used for ligand screening in order to work in a protein's "native environment"; the second argues that there is no reason to expect that the "most abundant" form of the protein under these conditions should be competent to bind

ligand.

However, these sentences are not necessarily contradicting. The first merely points out the fact that a huge advantage of NMR over other techniques such as protein crystallography is that NMR is done in solution rather which is the proteins native and relevant environment rather than finding a snap-shot of one of potentially many many different conformational states which is given by protein crystallography. The later statement is merely meant to draw on the fact that the most biologically relevant conformation of a protein may not be present all of the time, especially if that conformation requires co-factor or ligand binding which is required in order to induce a conformational change to said protein which results in the biologically relevant conformation.

Thus, it is asserted that the declaration and arguments presented by Prof. Gardner are unpersuasive to overcome the rejection of record.

Response to Arguments

7. Applicant's arguments filed 11 April 2008 have been fully considered but they are not persuasive.

Applicants contend that the prior art descriptions (including Fesik, WO 97/18471) of "SAR by NMR" wherein structure-activity relationships are obtained by NMR have targeted "druggable" proteins, apo-proteins, which are structurally characterized to have preformed ligand binding pockets. In contrast, PAS domains are determined to be absent any ligand binding pockets and thus said proteins would not have been

screened for ligand binding (see Remarks, p. 3, last two paragraphs and p. 4, first three paragraphs). It is asserted that PAS domains are considered "undruggable" because they are involved in protein/protein interactions.

However, it was known in the art at the time of filing that PAS domains were important signaling modules that monitor changes in light, redox potential, oxygen, small ligands, overall energy level and that the PAS domains indeed do have a tightly packed hydrophobic core (Taylor et al, 1999; pg 480, parg 1; pg 488, parg 3; pg 490, parg 2, 1st column). Thus, these proteins are not solely involved in protein-protein interactions as asserted. Rather, these proteins function with the assistance of a co-factor, for instance, the heme in FixL is utilized for oxygen sensing. With regard to the PAS domains being "undruggable" and that it would not be obvious to screen for ligands in the absence of preformed ligand binding cavities, the following paragraph addresses these concerns as Applicants have reiterated these statements and assertions throughout the Remarks.

Applicants further argue that the claims are indeed non-obvious and that the previous Office action overstates what Applicants are claiming (see Remarks, 5, 1st paragraph):

We believe that the Action construes our claims more broadly than intended: emphatically, we are not claiming a method of detecting PAS domain binding by NMR. Rather, our claims are strictly limited to detecting PAS domain binding of a particular type of PAS domain - one determined to have no NMR-apparent a priori formed ligand cavity, to a particular type of ligand - a foreign, hydrophobic core ligand. This double-requirement underlies the nonobviousness of our claim: if one skilled in the art was motivated to detect PAS domain hydrophobic core ligand binding, the last place he would look is a PAS domain that he had already confirmed had no NMR-apparent a priori

formed core ligand cavity.

However, Applicants are pointed to the decision by the Board of Patent Appeals and Interferences on p. 6 wherein the Board did not agree with Applicants position regarding this matter:

"Appellants contend that:

the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the art (*supra*) teaches squarely away from such use.

(App. Br. 5.)

We do not agree that "one skilled in the art would not have suspected that... PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding" (Appeal Br. 5). Takahaski suggests a method for identifying ligands for a PAS protein having a hydrophobic core (Answer 6). Edery also describes an assay method for identifying compounds that regulate a PAS domain protein's activity. Thus, despite the fact that these proteins have tightly packed cores with no pre-formed cavities - a fact that Appellants have not challenged - it was still suggested that these PAS domain proteins be utilized for ligand screening (see, e.g., Takahaski, at col. 9, ll. 14-16; Edery, at col. 46-50)."

Thus, it is asserted that given the state of the prior art and the motivation provided by the art of record to combine the teachings and have a reasonable expectation of success in doing so, that the instant maintained rejection provides a reasonable *prima facie* case which makes obvious the instant claimed methods.

It is noted that Applicants comments on p. 5, last two paragraphs, are acknowledged.

Conclusion

8. Claims 3 and 5 are rejected. Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).
Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suzanne M. Noakes/
Patent Examiner, Art Unit 1656
20 July 2008